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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,478	11/15/2006	Gordana Kosutic	014811-487.114US	8427

24239 7590 12/08/2010

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EXAMINER	
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ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
12/08/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,478	KOSUTIC ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/25/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1-3 are pending

The amendment filed 10/22/10 which amends claims 1 and 3 has been entered. Claims 4-13 were cancelled by the amendment filed 12/2/05. Claims 1-3 are under examination.

The ODP rejection of claims 1 and 2 over US 6713452 is withdrawn in light of that treatment of Paget's disease is not necessarily lead to treating pain since Pagets' disease often is painless is often painless (see "Arthritis Today" reference discussed below.

Priority

Applicant's claim [through amendment (filed 1/6/10) of the specification] for priority that instant application is a continuation-in-part of 10235284 filed 9/5/02 (now US Pat. No. 6770625), and is a continuation application (CON) of 10806523 filed 3/23/04 (now US Pat. No. 7084121) which is a CON of 09873777 filed 6/04/01 (now US Pat. No. 6713452), under 35 U.S.C. 120 is acknowledged.

However, neither 10806523, 09873777 nor 10235284 has adequate support for the disclosed method of treating peripheral pain using a mixture of conjugates comprising the first and second oligomers covalently linked to Lys^{11} and Lys^{18}, respectively, of salmon calcitonin (sCT). Thus, claims 1-3 are not granted priority to 6/04/01 the filing date of 09873777, nor 3/23/04 the filing of 10806523 nor 9/5/02 the filing date of 10235284. Yet, instant invention is entitled to the filing date 6/24/03 of provisional application 60482130, which has full support for claims 1-3.

The applicants' argument against "priority"

At pages 5-8, the response filed 10/22/10 discusses peripheral pain and central pain in general, and classification and characterization of the pain thereof, wherein the peripheral pain is termed

nociceptive which is initiated by nociceptor (pain receptor) which is responsible for bone pain experienced in osteoarthritis and Paget's disease as known in the art prior to filing of the instant application (p.7, paragraphs 2 and 3). The response asserts that US Pat. Nos.7084121 (10806523), 6770625 (10235284) and **6713452** (09873777) meet written description criteria (p.8, 3rd paragraph) which would allows instant application to be entitled to the benefit of the filing date of 10806523, 10235284 and 09873777.

Through discussion that Paget's disease is a peripheral aspect of bone pain, the response submits that later description of an *inherent* property, such as treating pain, does not deprive beneficial method (claims 1-3) of the filing date of an earlier application (p.8, 4th paragraph), and infers that information already known about peripheral pain relating to bone disease (e.g., Paget's disease) does not have to be disclosed in instant specification in order for considering that instant claims are entitled to the effective filing date 6/4/01 (p.8, 5th paragraph).

The applicants' arguments have been considered but are unpersuasive because, as discussed in page 3 of the previous Office action mailed 4/22/10, none of 10806523, 09873777 nor 10235284 discloses instant method of treating peripheral pain comprising administering to a subject in need thereof a mixture of conjugates (engineered sCT) comprising the first and second oligomers covalently linked to Lys^{11} and Lys^{18} of sCT polypeptide, and because the reasons below.

The later description (instant application) cannot substitute for the "*inherent* property", i.e., treating peripheral pain in the earlier applications, i.e., 09873777, 10806523 and 10235284 in view of "priority" discussed above.

MPEP (7.30.01) states that "*the specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention*". The inherency ("*inherent* property"), i.e., the relation of treatment of Paget's bone disorder to the treatment of the peripheral pain, cannot substitute "full, clear and concise" description of instant method in the specification of applications:10806523, 09873777 and 10235284 in order to consider the benefit of the earlier filing dates of said applications with regard to instant claims 1-3.

In the relative filed, it has been known that Page's disease is classified as a chronic bone condition that causes abnormal bone growth with common symptom bone pain (see WebMD (2010, updated) http://www.webmd.com/osteoporosis/tc/pagets-disease-of-bone-topic-overview, pages 1-4). The instant claims 1-3, however, are directed to treating "peripheral pain" (a large genus, claims 1 and 2) or "pain" (a large genus, claim 3) not bone disease such as Paget's disease.

Paget's disease is often painless though some population experience bone warmth and pain (see page 2, 2nd paragraph, Arthritis Today (2010, updated), http://www.arthritistoday.org/community/ expert-q--a/osteoarthritis/pagets-disease.php, pages 1-4). This suggests that treating Paget's disease cannot represent the treatment of pain.

US Pat. No. 6713452 (098737777) discloses use of PEGylated (at K^{11} and K^{18}) salmon calcitonin (sCT) polypeptide to treat a bone disorder such as osteoporosis, Paget's disease (patent claims 75-96). Yet, this patent is completely silent in disclosure of use said PEGylated sCT polypeptide to treat peripheral pain in a subject in need thereof as set forth in instant claims 1-3.

US Pat. No. 6770625 (10235284) discloses the pharmaceutical composition comprising the PEGylated (at K^{11} and K^{18}) salmon calcitonin (sCT) polypeptide (e.g., patent claims 56 and 57), and use said composition to treat a bone disorder (patent claim 62), and teaches that the bone disorder may be Paget's disease (col.39, lines 51-56). However, this patent fails to disclose use of the pharmaceutical composition to treat peripheral pain in a subject in need thereof as set forth in instant claims 1-3.

US Pat. No. 7084121 (10806523) discloses use of mixture of conjugate to treat a bone disorder such as osteoporosis, Paget's disease (patent claims 11 and 12), wherein said mixture of conjugate comprises the PEGylated (at K^{11} and K^{18}) salmon calcitonin (sCT) polypeptide (col.2, lines 49-61). Yet, this patent is completely silent in disclosure of use said PEGylated sCT polypeptide to treat peripheral pain in a subject in need thereof as set forth in instant claims 1-3.

The above three patents only disclose Paget's disease with the symptom of bone pain; this disease cannot represents a large genus "peripheral pain" which encompasses any types of pain which originate in muscles, tendons, bone and peripheral nerves as recognized by applicants (p.6, lines 5-7, the response). The peripheral pain (genus, set forth in claims 1-2) associated with diverse diseases/disorders, e.g., muscle pain (myalgia) a symptom of many diseases and disorders such as those due to viral infections, a metabolic myopathy, some nutritional deficiencies and/or chronic fatigue syndrome (Wikipedia (2010, updated) "*Myalgia*", http://en.wikipedia.org/wiki/Myalgia, pages 1-3). Moreover, the amended claim 3 now is directed to treating "pain" (even broader than the "peripheral pain" set forth in claim 3 amended). Thus, the treatment of Paget's disease symptom, i.e., bone pain, cannot adequately represent treatment of genus "peripheral pain" (claims 1-2), or genus "pain" (claim 3). The above-discussed three US patents lack adequate written description for instant method. Ttherefore, instant claims 1-3 are neither entitled to 6/04/01 the filing date of 09873777 (US6713452), nor 3/23/04 the filing of 10806523 (US 70841210) nor 9/5/02 the filing date of 10235284 (US 6770625).

IDS

The references cited in the information disclosure statement (IDS) filed 5/25/10 that have been considered by Examiner.

Withdrawal rejections and objection

[1] The 112/1 rejection (new mater) of claim 3 is withdrawn in light of amendment of claim 3.

[2] The 112/2 rejection of claims 1 and 3 is withdrawn in light of amendment of these claims.

[3] The objection of the specification is withdrawn in light of the amendment of the specification thereof.

Maintained-Claim Rejections - 35 USC §102(e)

The text of Title 35, U.S. C 102(e) not included herein can be found in the prior Office action mailed 3/4/09.

Claims 1-3 remain rejected under 35 U.S.C. 102(e) as anticipated by Soltero et al. (US 6770625 B2), wherein the fact of intense pain in bone disorder Paget's disease is evidenced by the Yamamoto et al. (US 5059587) (see col. 1, lines 64-65).

In patent claim 62, Soltero et al. teach a method of treating a bone disorder such as "Paget's disease" (see col. 39, lines 56). The method comprises orally administering to a subject in need a pharmaceutical composition comprising "calcitonin (CT)-drug-oligomer conjugate"; wherein CT is salmon calcitonin (patent claim 120-122) and wherein the conjugate is in a mono-dispersed mixture (patent claims 62, 76-79 and 81). Said "oligomer" preferably is "polyethylene glycol" (PEG) (see patent claim 80, and col. 24, lines 27, 35 and 36) linked to Lys^{11} and Lys^{18} residues of calcitonin (patent claim 79). Because intense pain is associated with "Paget's

disease", treating said disease would necessarily lead to treatment of the bone pain, a peripheral pain. Since salmon calcitonin (sCT) is unique, the sCT polypeptide inherently reads on instant SEQ ID NO:1. These teach instant method of claim 1.

Soltero et al. teach the structure: "Salmon calcitonin-[CO-$(CH_2)_7$-$(OC_2H_4O)_7CH_3]_2$" (see col. 31, lines 3-8) wherein "-$(OC_2H_4O)_7$" is PEG moiety subunits (see col. 25, lines 7-16, this meets the limitation 7 polyethylene glycol subunits), wherein the portion "CO-$(CH_2)_7$-" is a lipophilic moiety that preferably is a fatty acid moiety (see col. 25, lines 37-40), and wherein "**2**" in outside parentheses "[ ]" indicates that two residues of sCT peptide, i.e., Lys^{11} and Lys^{18}, are conjugated to the PEG moieties. This teaches the structural limitation of the "conjugate" of claim 3.

Soltero et al. teach that **a** (one) hydrolyzable bond between drug peptide and the "oligomer" (see col. 33, lines 47-50). In accordance with the claim 38 disclosure that PEG is coupled to the "oligomer" (i.e., calcitonin) via Lys^{11} and Lys^{18} residues of calcitonin, thus, one of these two ε-lysine amino groups is conjugated to the PEG through said "hydrolyzable bond" while the other remains non-hydrolysable. This meets the structure of claim 2 "conjugate". Therefore, Soltero et al. inherently teach the method of claim 2.

The applicants' response to the above 102(e) rejection

At page 10, the response filed 10/22/10 argues that the claims priority date being 6/4/01 would obviate the rejection. This is unpersuasive because, as discussed in the above "priority" section, instant claims are entitled to the filing date 6/24/03 of provisional application 60482130 but not 6/4/01. Thus, the 102(e) rejection stands.

Claim Rejections - 35 USC §103(a)

The text of Title 35, U.S. C 103(a) not included herein can be found in the prior Office action mailed 3/4/09.

[1] Claim 1 remains rejected under 35 U.S.C. 35 U.S.C. 103(a) as unpatentable over as obvious over Lee et al. (US 6506730 B1).

In patent claims 1 and 2, Lee et al. teach a method of treatment a disease comprising administering to mammal in need a pharmaceutical composition comprising polyethylene glycol (PEG) conjugated (PEGylated) calcitonin peptide wherein said calcitonin is obtained from Salmon (see Example 1, wherein Salmon calcitonin is termed "sCT"), and wherein the treatment refers to curing Paget's disease (instantly claimed "Pain" (genus) or "peripheral pain" (genus) encompasses the Paget's disease-caused bone pain) which common symptom is bone pain - a peripheral pain which is resulted from the bone absorption and osteoporosis (see col. 6, line 24-28). The PEGylation occurs at Lys^{11} and Lys^{18} of calcitonin (see col.5, line 54 and also Example 4 "di-PEG-sCT"), i.e., di-PEG calcitonin. Lee et al. teach a uniformed PEG-peptide conjugate wherein "uniformed" conjugate is equivalent to instant "mono-dispersed mixture conjugate". The sCT is a single chain peptide of 32 amino acids (col.6, lines 23-25). Since calcitonin from a particular species, herein, the species is Salmon, must have unique amino acid sequence, the sCT inherently reads on instant SEQ ID NO:1. These are applied to instant claim 1.

Provided that Lee et al. do not expressly teach use oral administering route including oral transmucosal administration.

It would have been obvious to one skilled in the art at the time the invention was made to determine the administration route, and/or parameters for suitable/optimal administration. Injection administration gives patients pain and has accompanying dangers; and thus, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development and determination are well within the purview of one skilled in the art. One of ordinary skill in the art would have TRIED the other administration route such as oral administration rather than the injection. In addition, transmucosal delivery (including oral transmucosal delivery) has been suggested (col.1, lines 55-56). Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

The applicants' response to the above 103 rejection

At pages 10-13, the response filed 10/22/10 submits that the sCT taught by Lee et al. is mono-conjugated (mono-PEGylated) at Lys^{11} or Lys^{18} not both PEGylated via showing Fig.2 and Example 4 thereof.

The response asserts that Lee et al. teach away the oral administration route set forth in claims 1-3, and that Lee et al. discuss advantage of nasal "transmucosal route" over oral route (p.12, the response). Thus, the response infers that the Lee et al. teaching regarding said advantage would discourage a skilled artisan from using the oral route; and therefore, requests withdrawal of the 103 rejection (p.13, lines 1-4).

The applicants' arguments are found unpersuasive because of the reasons below.

Lee et al. teach di-PEG-sCT (see Fig.1, and col.4, lines 32, Example 4, col.9, line 15) and teach PEGylated at both Lys^{11} and Lys^{18} (are used (see col.5, lines 42-44 and 53-54).

Instant claim language "orally administering" set forth in claims 1-3 as written encompasses "oral transmucosal administration" as is evidenced US 2004/0034059 A1 (see [0013], line 3). Although Lee et al. discuss the advantage of the nasal transmucosal route, one of ordinary skill in the art (pharmacology) would have meanwhile recognized the PEGylated sCT has increased in-vivo half life span and solubility (col.3, lines 16-19) which allows one of ordinary skill in the art to try oral transmucosal administration because it is more convenient than nasal transmucosal delivery, and would have modified or designed "other embodiments for carrying out the same purpose of the present invention" as taught by Lee et al. (col.12, lines 45-

49), wherein said "other embodiment" refers to other administration route discussed at col.1, lines 43-48, Lee et al. Thus, it would have been obvious to try oral transmucosal delivery of the PEGylated sCT for treating the pain in a patient.

[2] Claim 1 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that calcitonin (CT) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21). Russo does not expressly teach use PEGylated CT for treating pain, e.g., hypercalcemia pain, wherein PEGylation includes PEGylation at Lys^{11} and Lys^{18} residues of CT (claim1), nor expressly teach oral administering route.

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) at Lys^{11} and Lys^{18} residues and teach advantages of the PEGylation of enhance stability, increases half-life and decrease immunogenicity of said sCT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1, as applicable to claim 1.

Provided that Russo and Komarova et al. do not expressly teach oral administration route for treating pain.

Lee et al. teach that injection administration gives patients pain and has accompanied dangers; and thus, there is a need to develop other routes for peptide administration (col. 1, lines 43-48).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the PEGylated sCT for treating the pain condition, wherein the PEG moiety is conjugated to the sCT peptide directly through amino acids Lys^{11} and Lys^{18}. This is because

Russo has taught usefulness of sCT peptide for treating pain, and becasue Komarova et al. have taught that the sCT peptide is PEGylated at of Lys^{11} and Lys^{18} side chains. This Pegylation has advantage over the unpegylated peptide thereof in enhanced stability, increases half-life and decreased immunogenicity (see above). Thus, it would have been obvious for one of ordinary skill in the art to substitute the PEGylated sCT for the non-PEGylated thereof with reasonable expectation of success.

In addition, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration or oral transmucosal delivery rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected results. Therefore, the combination of references' teachings above renders the claims obvious.

The applicants' response to the above 103 rejection

At page 13, the response filed 10/22/10 argues that Komarova reference is published on 6/6/03; as such, said reference is not competent prior art as instant claims have an effective filling date 6/4/01. Also, the response asserts Lee et al. teach away the oral administration route.

The applicants' arguments are found unpersuasive because, as discussed in the above "priority" section, instant claims are only entitled to the filing date 6/24/03 but not 6/4/01.

The PEGylated sCT taught by Lee et al. has increased in-vivo half life span and solubility (col.3, lines 16-19) which allows one of ordinary skill in the art to try oral transmucosal administration because it is more convenient than nasal transmucosal delivery, and would have modified or designed "other embodiments for carrying out the same purpose of the present invention" as taught by Lee et al. (col.12, lines 45-49), wherein said "other embodiment" refers to other administration route discussed at col.1, lines 43-48, Lee et al. Thus, it would have been obvious to try oral transmucosal delivery of the PEGylated sCT for treating pain in a patient. It is of note that Instant claim language "orally administering" set forth in claims 1-3 as written encompasses "oral transmucosal administration" as is evidenced by US 2004/0034059 A1 (see [0013], line 3).

Thus, the 103 rejection is proper and maintained.

[3] Claim 2 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73, 265-273), Katre at al. (US Pat. No. 4917888) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that calcitonin (**CT**) has therapeutic application for relieve pain such as "hypercalcemia pain" (see col. 9, lines 18-21).

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) and the advantages of the PEGylation: enhance stability, increases half-life and decrease immunogenicity of said CT peptide, wherein PEGylation occurs at Lys^{11} and Lys^{18} side chains of the CT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1. The Russo and Komarova teachings are applied to claim 2.

Provided that Russo and Komarova et al. do not expressly teach attachment of a non-hydrolysable linker between the peptide PEGylated and polyethylene glycol (PEG) nor expressly teach oral administration.

Katre et al. teach the hydrolysable bond between amine group of lysine and PEG moiety in the PEGylated peptide IL-2 (see col. 14, lines 28-36) wherein the amine group is lysine side chain (col. 8, lines 41-44).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to introduce a hydrolysable linker or bond between the peptide and PEG moiety. This is because Russo has taught usefulness of sCT peptide for treating pain, and Komarova et al. have taught that the PEGylated sCT peptide is advantageous over the unpegylated peptide at least in three aspects: enhanced stability, increases half-life and, and decreased immunogenicity.

The hydrolysable bond between the PEG moiety and lysine amino side chain offers an advantage, i.e., it is particularly useful for recovering the peptide from the chromatographic column wherein the pH value of said column is close each other to that render the bond susceptible to hydrolysis as taught by Katre et al. (see col. 14, lines 28-36). Thus, one of ordinary skill in the art would have extended the Katre's results into production of the PEGylated sCT peptides. The produced PEG-sCT conjugates would expect to have benefit that the PEG polymer cane be removed under alkaline condition and thus the sCT peptide can be recovered from the hydrolysis.

In addition, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen

unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

Therefore, the combination of references' teachings renders claim 2 obvious.

The applicants' response to the above 103 rejection

Similar to argument of the 103(a) rejection [2] above, the response filed 10/22/10 asserts that Komarova reference is not competent prior art in view of that instant claims have an effective filling date 6/4/01 (p.13, last paragraph).

The response submits that neither Russo nor Lee et al. teach PEGylation at both sites Lys^{11} or Lys^{18}, and that Lee et al. teach away the oral administration. In addition, Katre et al. do not overcome defect of the three references Russo, Komarova et al. and Lee et al. (p.13, last paragraph). As such, the response request withdrawal of the 1093 rejection.

The applicants' arguments are found unpersuasive because, as discussed in the above "priority" section, instant claims are only entitled to the earliest filing date 6/24/03 but not 6/4/01.

Komarova et al. have taught use of the PEGylated at both residues Lys^{11} or Lys^{18}. the discussion of the "oral transmucosal administration route has been set forth above. Katre et al. provide the teaching regarding hydrolysable bond between amine group of lysine and PEG moiety in a PEGylated peptide. The motivation of combination of the references teachings has been set forth in the above rejection. Thus, the 103(a) rejection of claim 2 is proper and maintained.

[4] Claim 3 remains rejected under 35 U.S.C. 103(a) as unpatentable over as obvious over Russo A. F. (US Pat. No. 5976788) in view of Komarova et al. (*Calcif. Tissue Int.* (2003, online published on 6/6/03) 73,265-273), Katre et al. (US Pat. No. 491788), Crotts et al. (US 2003/0017203 A1), Ekwuribe N. (US Pat. No. 6638906 B1 cited in the Office action mailed 3/4/09) and Lee et al. (US Pat. No. 6506730 B1).

Russo teaches that CT therapeutic use in relieving pain, e.g., "hypercalcemia pain" and treating Paget's disease (col. 9, lines 17-21).

Komarova et al. teach PEGylation of Salmon calcitonin (sCT) peptide (Fig. 1) and the advantages of the PEGylation: enhance stability, increases half-life and decrease immunogenicity of said CT peptide, wherein PEGylation occurs at Lys^{11} and Lys^{18} side chains of the sCT peptide (see p.265, right col., 2nd paragraph, and Fig. 1), wherein the amino acid sequence depicted in Fig.1 has 100% sequence identity to instant SEQ ID NO:1.

These are applied to claim 3.

Provided that Russo and Komarova et al. do not expressly teach attachment of a carboxylic acid as a linker between the peptide and PEG, nor expressly teach oral administration.

Ekwuribe teaches incorporation of a carboxylic acid such as fatty acid (see col. 11, lines 7-8) into between PEG moiety and the PEGylated peptide in order to enable better penetration of the PEGylated peptide through the cell membrane, which is mimic penetration enhancer (see Example section at col. 11, lines 28-32, and lines 37-40 and col. 6, lines 60-67). Ekwuribe further teaches that lipophilic (hydrophobic) portion of fatty acid is distal to the point of attachment to the LCRE peptide (col. 11, lines 7-8); this is an obvious structural variation of the

claim 3 limitation as to carboxylic acid is coupled at the end distal to the carboxylic acid moiety to PEG moiety.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate a fatty acid (a type of "carboxylic acid) into PEG conjugated the sCT peptide between the conjugation sites: Lys^{11} or Lys^{18} of said peptide and the PEG moieties. This is because Russo has taught usefulness of sCT peptide for treating pain, and Komarova et al. have taught that the PEGylated sCT peptide is advantageous over the unpegylated peptide in at least three aspects: enhanced stability, increases half-life and, and decreased immunogenicity.

It has been known that a biological difficulty for salmon sCT to penetrate the mucus membranes which limits bioavailability of the calcitonin (see [0004], lines 11-15, Crotts et al.). Upon reading the Crotts and Ekwuribe reference, one skilled in the art would have realized the problem of bioavailability of the calcitonin peptide caused by the membrane penetration, and realized that bioavailability of the calcitonin peptide caused by the membrane penetration of said peptide, and realized that the incorporated fatty acid in the PEGylated peptide wherein the fatty acid acts as membrane penetration enhancer is beneficial for the PEGylated sCT peptide; and would have known that the incorporation of fatty acid which is known membrane anchor molecule. Ekwuribe has addressed that their inventions is not limited to the "LCRF" peptide but applicable for other therapeutic peptides (see col. 8, lines 30-37), e.g., the sCT peptide herein. Thus, one of ordinary skill in the art would have modified the PEGylated sCT peptide further to incorporate fatty acid (a carboxylic acid) into said peptide in order to improve the membrane penetration ability of the PEGylated sCT.

Additionally, considering that seeking for other administering route other than painful injection administration as taught by Lee at al., and further considering that Russo's invention is directed to reducing pain, one of ordinary skill in the art (physician) would have chosen unpainful route such as oral administration which is well within the purview of one skilled in the art. Since the injection gives patients pain and has accompanying dangers, there remains a need to develop other routes for peptide administration (col. 1, lines 43-48, Lee et al.). Said development or determination is well within the purview of one skilled in the art. One of ordinary skill in the art would have tried the other administration route such as oral administration rather than the injection. Therefore, said oral administration is considered to be prima facie obvious in the absence of any unexpected result.

Therefore, the combination of references' teachings renders claim 3 obvious.

The applicants' response to the 103 rejections

At page 14, the response filed 10/2210 argues against the above 103 rejection similar to the applicants' arguments for the 103 rejections [2] and [3] set forth above. Additionally the response argues that Crotts et al. do not overcome shortcomings of Komarova, Uusso and Lee references. Thus, the response requests withdrawal of the rejection.

The reasons of unpersuasiveness of the applicants' arguments have been set forth accordingly under Examiner responses to the 103 rejections [2] and [3] above, because the applicants' argument herein is similar to the arguments as to the rejection [2] and [3] thereof. As for Crotts' reference concerned, Crotts et al. provide teaching as to the motivation of coupling fatty acid to sCT peptide in order to improve penetration of sCT through mucus membrane (see above). Thus, the combination of references' teachings renders claim 3 obvious, and therefore, the 103 rejection above is maintained.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

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December 6, 2010